Present treatment of rectal adenocarcinoma

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Improvement since 30 years. Surgery is the main treatment

Surgery is the basic treatment of rectal adenocarcinoma. Within the past 30 years post operative death has decreased from 10% to less than 4%. Permanent colostomy went down from 80% to less than 40%. The standard surgical approach is now sharp dissection of the mesorectum under direct vision called "TME" (Total Mesorectal Excision) surgery¹. The 5 year overall has increased from 45 to 60%. Rectal adenocarcinoma that was considered as a radioresistant tumor is now treated with preoperative External Beam Radiation Therapy (EBRT) in most of cases².

Perirectal and hypogastric nodal metastasis.

The Japanese work shows that the rate of perirectal Lymph Nodes (LN) varies from 13% in pT1 lesions to 64% in pT3. There is no hypogastric LN metastases in pT1-2 and 11% in pT3 tumors. When hypogastric LN are involved the survival at 5 years is close to zero percent³. There is at present time no reliable imaging technique to diagnose before surgery the N stage. May be MRI with specific contrast magnetic product will be relevant. Endorectal sonography is reliable to distinguish between T2 and T3⁴. The definition of T4 is still rather subjective.

Circumferential Rectal Margin (CRM)

Since the work of Quirke⁵ and the Dutch Colorectal group TME trial⁶, the CRM appears as an important end point to predict for local failure and distant metastases when it is involved on the pathological specimen. The definition of CRM R1 varies from 0 to 2 mm according institutions. The use of MRI appears interesting to identify before treatment patient at risk of CRM R1⁷.

Adenocarcinoma is a moderately radiosensitive disease

Radiotherapy alone in a preoperative schedule can provide complete sterilisation of T2-3 rectal adenocarcinoma in 5 to 15%. When used alone with very high dose thanks to endocavitary irradiation (contact X-Ray+/-iridium brachytherapy) control of 90% of T1N0 lesions is possible. In inoperable patients a combination of EBRT (small posterior pelvic volume) and endocavitary irradiation is able to control 60 to 80% of T2-3 lesions and most of all sterilize subclinical perirectal lymph nodes^{8, 9}.

Recent improvements in surgery

All the surgeons agree that the standard technique of surgery in "TME surgery" aiming at the sharp dissection of the rectum to avoid as much as possible a CRM R1. In the same time great care is taken not to section the hypogastric and presacral nerve which are of importance for urinary bladder and sexual function. Sphincter preservation is possible in many cases with colorectal very low anastomoses. A margin of 2 cm below the gross tumor is accepted by most surgeons. Reservoir may be useful during the first year after surgery to improve anal function. Intersphincteric dissection can further increase sphincter preservation but often leads to poor anal function. Local excision for T1 lesion or after preoperative EBRT for T2 or small T3 may gain interest in the near future.

Can we improve over surgery alone?

Many end points are relevant. The major one is overall survival but it takes many years to analyse. Disease free survival is a good indicator of overall survival. Local control is important because a high rate of local failure decreases the chance of cure and is responsible for very distressful symptom. Sphincter preservation is for all the patients a very serious concern. Improving sphincter preservation must not be at the price of an increase in local relapse or poor anorectal function and deteriorated quality of life mainly social life. Toxicity of adjuvant treatment is important. Care must be taken not to increase operative death or poor anorectal function.

From postoperative radio(chemo)therapy to preoperative radiotherapy

In 1990 American clinical Trials demonstrated that despite significant toxicity postoperative radiotherapy (45-50.4 Gy)

and concurrent continuous infusion of Fluorouracil with folinic acid was able to improve local control and overall survival. Since these works three trials (Uppsala, NSABP 03 and the German CAO/ARO/AIO) have proven that preoperative radiotherapy or radiochemotherapy is less toxic and give better local control than a postoperative schedule^{10, 11, 12}. It may also increase the chance of sphincter preservation if there is an interval of 4 weeks or more after EBRT. The Swedish Trial has proven that preoperative EBRT with a short schedule (25 Gy/5 day) can increase local control and overall survival¹³. But all these trials were done without standard TME surgery. The merit of the DCRCG TME trial is to demonstrate than even with TME preoperative EBRT (25 Gy/5 days) improves local control but not survival. At 5 years the local failure rate is 11.3% with TME alone and 5.8% with preoperative EBRT ($p=0.001$).

The role of concurrent and adjuvant chemotherapy.

Two randomised Italian and Dutch Trials with 5FU and folinic acid adjuvant chemotherapy has failed to demonstrate a survival benefit. It is possible that the adjuvant benefit from 5FU is different between Colon and Rectum cancer¹⁴. Two randomised Trials (EORTC 22 921 and FFCD 92 03) initiated in 1993 have been closed in 2003. Both Trials randomised in T3-4 M0 rectal cancer preoperative EBRT (45Gy/5 weeks) alone vs the same EBRT and concurrent chemotherapy (5FU+Folinic acid). Preliminary results of these two trials show an increase in early toxicity with the combined treatment but no increase in postoperative death¹⁵. The FFCD 92 03 trials shows a significant increase in complete pathological response (sterilisation) from 3 to 10% but no difference in sphincter preservation (51%). In 2004 taking into consideration these data preoperative radiotherapy alone should be considered standard for T3 and resectable T4 (and low T2) tumors. The best regimen between 25Gy/5 days and 45 Gy/5 weeks is not known although many radiation oncologists feel that 45 Gy is less toxic. The benefit of concurrent chemotherapy is not yet proven.

Future improvements

Sphincter preservation is an end point of great clinical reference. Two Lyon randomised Trials tend to show that a long interval of 4 weeks or more after EBRT can increase sphincter preservation¹⁶ and that a dose escalation using contact X-ray increases significantly sphincter preservation with the possibility in some patients to perform only a trans anal excision. On the opposite a Polish Trial failed to demonstrate a benefit of 50 Gy/5 weeks + chemo long interval vs 25 Gy/5 days immediate surgery.

Many phase I and II trials show encouraging results in term of tumor response and operative regimen sterilisation using concurrent EBRT (45 Gy-50 Gy/5-6 weeks) and Oxaliplatin, Capecitabine, Irinotecan and other biomodulators. The Xelox combination (Oxaliplatin and Capecitabine) appears promising to many authors^{17, 18}. Future phase III trials will try to show an improvement with preoperative concurrent chemoradiation. Local control which is close to 5% in the DLRCG trial is not any more the major endpoint. Adjuvant chemotherapy will in a near future become a major question regarding liver metastases and overall survival.

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